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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/333,680	11/03/94	WANG Q	CELL16

EXAMINER	
RORIES, C	
ART UNIT	PAPER NUMBER
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 11/12/97

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) _____ is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☑ Claim(s) _____ is/are allowed.
☑ Claim(s) _____ is/are rejected.
☐ Claim(s) 5 is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☑ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

★ U.S. GPO: 1998-404-496/40517

Claims 51, 53, and 55 are cancelled, claims 39, 46-50, and 54 are amended, and new claims 56 and 57 are added, as requested in the amendment filed 11/12/97. Claims 37-50, 52, 54, 56, and 57 are now pending in the application and have been examined.

The finality of the Office action mailed 7/11/97 is withdrawn because further consideration of the prior art has shown it to be necessary to reject claims 40-44, drawn to a plasmid comprising an inducible promoter linked to an adenoviral E4 early gene region, as being obvious to make and use at the time the application was filed.

The rejection of claims 39 and 48-50 under 35 U.S.C. § 112, first paragraph, because the specification is only enabling for the claimed invention wherein the recited packaging cell line is a 293-derived cell line, is withdrawn in view of the amendment filed 11/12/97.

Claims 46, 48, 49, and 54 remain rejected, and new claims 56 and 57 are newly rejected, under 35 U.S.C. § 112, first paragraph, because the specification is enabling for the claimed invention wherein the recited recombinant adenoviral vector is deficient in E1 and E4 early gene regions, but has a functional E2A early gene region, and wherein the recited packaging cell line is stably transformed with an expression construct comprising an inducible promoter linked to adenoviral E4 early region genes, for rescue of recombinant adenovirus lacking functional E1 and E4 early gene regions, but is not also transformed with an expression construct directing expression of E2A early region genes, for the reasons presented in the previous Office action.

The rejection of claims 39 and 48-50 under 35 U.S.C. § 112, first paragraph, because the specification is only enabling for the claimed packaging cell line wherein the nucleic acid sequence

in said cell line which supplies the function of the E4 early region is operably linked to an inducible promoter, is withdrawn in view of the amendment filed 11/12/97.

The rejection of claims 46-50 and 54 under 35 U.S.C. 112, second paragraph, that appeared in the last office action has been withdrawn in view of the amendment filed 11/12/97.

Claims 39, 41-44, 48-50, 54, and 57 are newly rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 39, 48-50, and 54 are indefinite because it is unclear what is meant by recitation of a "function" operably linked to a promoter.

Claim 39 is also indefinite because it is unclear how the recited "virus-associated RNA sequences" are related to the other elements of the invention recited in the claim.

Claims 41-44 are indefinite in their recitation of "the cAMP response element," "the gene encoding ... alpha inhibin," and "the gene encoding the tetracycline responsive promoter," because use of the definite article "the" incorrectly suggests that there is only one of each type of the recited elements.

The statement that claims 40-44 are allowable over the prior art of record in the previous Office action is withdrawn because further consideration of the claimed subject matter and of the prior art has made it apparent that it would have been obvious to make and use the claimed plasmids to express E4 genes in transiently transfected cells, even if doing so was expected to be toxic to the cells, as discussed below.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 40, 42, and 43 are rejected under 35 U.S.C. § 103 as being unpatentable over Ketner et al., in view of Jyan-Gwo et al.

Ketner et al. disclose plasmids comprising a promoter operably linked to a DNA molecule comprising one or more of the open reading frames (ORFs) of the adenoviral E4 early region, and a method wherein the plasmid is transiently transfected into cultured mammalian cells so that the protein(s) encoded by the E4 region ORFs are produced in the cells, in order to identify E4 ORFs which are essential for adenoviral replication (pp. 3038-3045). Ketner et al. do not disclose plasmids wherein the promoter linked to the DNA comprising adenoviral E4 early region ORFs is an inducible promoter such as a promoter from a murine α-inhibin gene, which comprises a cAMP response element (CRE) and is induced by an agent which increases cellular cAMP concentration.

Jyan-Gwo et al. disclose a plasmid comprising a luciferase reporter gene linked to a promoter from a murine α-inhibin gene, and teach the promoter is induced to stimulate expression of the linked reporter gene in a cell that is treated with forskolin, an adenyl cyclase activator (pp. 288-289).

At the time the application was filed, it would have been obvious to one of ordinary skill in the art to follow the teachings of Ketner et al. to make plasmids comprising a promoter operably linked to a DNA molecule comprising ORFs of the adenoviral E4 early region, for use in identifying the ORFs required for adenoviral replication, as discussed above, and to make instead plasmids comprising a promoter from a murine α-inhibin gene, for stimulated expression in cells treated with an activator of adenyl cyclase as taught by Jyan-Gwo et al. as discussed above, given the recognition by those of ordinary skill

in the art that plasmids comprising a promoter from a murine α-inhibin gene would reasonably have been expected to function successfully in forskolin-treated cells to direct expression of the E4 region ORFs in the same effective manner shown for the plasmids comprising non-inducible promoters as taught by Ketner et al. as discussed above, and given the recognition by those of ordinary skill in the art that choice of promoter used to obtain expression of the E4 ORFs for identification of ORFs required for adenoviral replication, would have been optimization of process parameters. Thus, the invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Claim 44 is rejected under 35 U.S.C. § 103 as being unpatentable over Ketner et al., in view of Jyan-Gwo et al. as applied to claims 40, 42, and 43 above, and further in view of Gossen et al.

Ketner et al., in view of Jyan-Gwo et al. teach making a plasmid comprising an inducible promoter operably linked to a DNA molecule comprising one or more ORFs of the adenoviral E4 early region, for use in identifying the ORFs required for adenoviral replication, as discussed above; however, they do not teach making such a plasmid wherein the promoter is a tetracycline-responsive promoter.

Gossen et al. disclose a plasmid comprising a tetracycline-inducible promoter operably linked to a luciferase reporter gene, and show that the promoter is induced by tetracycline to give high levels of expression of the linked gene in mammalian cells which are co-transformed to produce a tetracycline-responsive transactivator protein (pp. 5547-50).

At the time the application was filed, it would have been obvious to one of ordinary skill in the art to follow the teachings of Ketner et al., in view of Jyan-Gwo et al., to make a plasmid comprising an inducible promoter operably linked to a DNA

molecule comprising one or more ORFs of the adenoviral E4 early region, for use in identifying the ORFs required for adenoviral replication, as discussed above, and to modify those teachings by making a plasmid comprising a tetracycline-inducible promoter operably linked to the E4 region ORFs, to obtain high, tetracycline-induced levels of expression of the linked adenoviral genes in cultured mammalian cells as taught by Gossen et al., given the recognition by those of ordinary skill in the art that a plasmid comprising such a tetracycline-inducible promoter would reasonably have been expected to function successfully in tetracycline-treated cells comprising said tetracycline-responsive transactivator protein to direct expression of the E4 region ORFs in the same effective manner shown for the plasmids comprising non-inducible or forskolin-inducible promoters as taught by Ketner et al., in view of Jyan-Gwo et al., as discussed above, and given the recognition by those of ordinary skill in the art that choice of promoter used to obtain expression of the E4 ORFs for identification of ORFs required for adenoviral replication, would have been optimization of process parameters. Thus, the invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

Claim 45 is allowable over the prior art of record because at the time the application was filed, there was no suggestion in the prior art to make a plasmid having the same construction and nucleotide sequence as that of the recited plasmid.

Claims 37-39 and 46-55 are allowable over the prior art of record, because at the time the application was filed, it was unpredictable whether or not a cell line transformed to contain functional genes encoding both the E1 and E4 adenoviral early region genes would survive and grow. Applicants' successful demonstration that 293 cells stably transformed with an

expression construct comprising an inducible promoter linked to the adenoviral E4 early region genes would survive, grow, and efficiently produce recombinant adenovirus with deletions in both E1 and E4 regions was an unexpected and unobvious result.

Claims 37, 38, 45, 47, and 52 are allowable.

The Declaration of Dr. Wang under 37 C.F.R. § 1.132 filed 11/12/97 is insufficient to overcome the rejections of claims based upon 35 U.S.C. § 112, first paragraph, because the declaration is not signed and therefore is improper.

Applicant's arguments filed 11/12/97 have been fully considered but they are not deemed to be persuasive.

Applicants urge that rejection of claims 46, 48, 49, and 54 under 35 U.S.C. § 112, first paragraph, for failure to adequately teach how to use the invention, be reconsidered and withdrawn, because the specification is only enabling for the claimed invention wherein the recited recombinant adenoviral vector is deficient in E1 and E4 early gene regions, but has a functional E2A early gene region, and wherein the recited packaging cell line is stably transformed to complement E1 and E4 early gene regions, but is not also transformed to complement E2A early region genes, because the Declaration of Dr. Wang under 37 C.F.R. § 1.132 filed 11/12/97 provides evidence that the specification also enables the claimed invention wherein the recited recombinant adenoviral vector is deficient in an E2A early region gene, and wherein the recited packaging cell line is stably transformed to complement the non-functional or missing E2A early region gene.

The examiner maintains that rejection of the claims is proper in the absence of a proper Declaration under 37 C.F.R. § 1.132 proving enablement of the claimed invention, and that the

Declaration of Dr. Wang under 37 C.F.R. § 1.132 filed 11/12/97 is insufficient to overcome the rejections of claims based upon 35 U.S.C. § 112, first paragraph, because the declaration is not signed and therefore is improper, as stated above.

General Information Regarding Further Correspondence

Any inquiry concerning this or earlier communications from the examiner should be directed to Dr. Charles Rories, Group 1800, Art Unit 1819, at telephone number (703)-308-1120. The examiner can normally be reached from 7:30 AM to 5:00 PM on Monday-Thursday and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine Chambers, can be reached at (703)-308-2035.

Papers related to this application may be submitted to Art Unit 1819 in Crystal Mall I by facsimile transmission to telephone number (703)-305-4242 or (703)-305-3014. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Any inquiry of a general nature or relating to the status of this application, should be directed to the Group 1800 receptionist, at telephone number (703)-308-0196.

9 December 1997

Charles C. P. Rories
Patent Examiner
Art Unit 1819